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Title **Testing for HER2 Positive Breast Cancer. Challenge for Improvement of Current Conditions and Practice**

Agency **LBI of HTA, Ludwig Boltzmann Institute of Health Technology Assessment**
Garnisongasse 7/20, AT-1090 Vienna, Austria;
Tel: +43 1 236 8119 0, Fax: +43 1 236 8119 99; office@hta.lbg.ac.at, http://hta.lbg.ac.at

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Aim

To address the following questions: Are the resources allocated to treat HER2 patients being used most efficiently? What is the gold standard for diagnosing HER2-positive tumors? Which method is most accurate and reproducible in identifying candidates for potential therapy with monoclonal antibodies, and are the tests reliable for selecting HER2-positive patients? Is it necessary to look closer at specific areas of uncertainty – if so, which areas?

Conclusions and results

The review systematically discusses HER2 testing results of more than 23 000 specimens (in local, central, or reference labs) explored by different testing methods (DNA, RNA, protein levels).

- Many studies are not comparable due to differences in specimen numbers, tissue extraction, specimen histology, and test methods.
- IHC (immunohistochemistry) results show more variability than FISH (fluorescence in situ hybridization) results, particularly in FISH-negative cases. The results of most studies indicate that high-level HER2 amplification and an IHC score of 3+ will identify HER2-positive breast carcinoma; low-level amplification and/or IHC score of 2+ should be carefully interpreted.
- There is agreement that the most (cost-) effective testing strategy is to screen all patients with IHC, followed by FISH for IHC of 2+ (or of 2+ and 3+).
- A challenge in routine practice concerns differences in interpreting probes. There is a need to adhere to guidelines in handling disconcordant results and validation of clinical results.
- Uncertainty exists regarding the clinical significance of low-level gene amplification in the response to trastuzumab.
- Findings concerning different results from local/central labs point to moderate inter-observer and inter-laboratory reliability of test results. A volume/experience relationship is observed.
- Inter-laboratory comparisons and performance evaluations are important in overcoming test limitations. The results of this assessment suggest there are fewer HER2-positive women than generally reported: not 20% to 30%, but 15% to 20% are amplifying HER2 positive in "real-life" settings.

Recommendations

- Due to the high variability between the different IHC tests, we recommend using only standardized and approved tests.
- Due to the consequential costs (non-monetary costs/side effects of therapy and monetary costs), we recommend establishing standard operating procedures.
- Due to high inter-laboratory variability, we recommend using a few central reference centers.
- Due to high inter-laboratory variability, we recommend national and international inter-laboratory exchange on results of diagnostic outcome.

Methods

We searched the literature in several databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Pascal Biomed, and BIOSIS Previews) and included studies (n=75) published after year 2000. The main focus was on issues of validity, standardization and/or calibration of the two most commonly used methods (IHC and FISH), inter-observer and inter-laboratory concordance, and the role of the morphological variables and borderline test results.

Written by Korencan A and Wild C, LBI of HTA, Austria

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